REMARKS

Reconsideration of the rejections set forth in the Office action mailed March 22, 2005 is respectfully requested. Claims 1-6 and 9 are currently pending in this reissue application.

I. Claim Status and Current Amendments

Claims 1-6 and 9 are currently pending in this reissue application. Claims 7, 9 and 11 were previously cancelled, and claims 10, 12 and 13 are cancelled by this amendment.

The phrase "a uniform population of substantially identical oligonucleotide tag complements" in claim 1 is amended for clarity to "a population of identical oligonucleotide tag complements".

Claim 4 is amended to correct a typographical error pointed out by the Examiner.

Claims 5 and 9 are amended to recite that "each microparticle has identical polynucleotides of the plurality attached thereto". This is supported in the specification at, for example, column 3, lines 55-56 of the '413 patent, which states that "subpopulations of identical polynucleotides are sorted onto particular beads or regions".

The language of dependent claim 6 is amended to comport more closely with that of parent claim 5.

Claim 9 is further amended, for clarity, to replace "wherein tag complements are attached to each of said microparticles of said mixture, and wherein each of said cDNAs or said fragments of said plurality..." with "wherein tag complements are attached to each said microparticle, and wherein each said cDNA molecule or fragment.

Claims 10, 12 and 13 are cancelled.

No new matter is added by any of the amendments.

II. Amendment Format

The Examiner stated, on page 3 of the current Office Action, that previous amendments to the claims had been entered in a format which was improper for a reissue application; that is, with changes indicated relative to the previous version of the claims, rather than to the issued '413 patent.

However, to applicants' understanding, the previous response did submit the amended

claims in the proper reissue format (with the exception of status indicators such as "Twice Amended"). The following is a quotation from page 8 of the previous response, filed October 7, 2004 (emphasis added):

> "The substitute specification, including claims, which is enclosed herein *includes the pending claims with changes indicated relative to the patent specification in effect as of the date of filing of the reissue application, in accordance with MPEP §1453*. Changes are indicated by underlining of added material, i.e., the entire text of each of claims 5-13, with the exception of claim 7, which was cancelled in the amendment submitted on February 10, 2001, and claim 8, which is cancelled with this response."

The previous response also stated the following, in the section entitled "Amendments to the Claims" (page 2):

> "The enclosed claim pages provide the amended claims in the proper format for a reissue application, showing changes relative to the patent specification in effect as of the date of filing of the reissue application, in accordance with MPEP §1453.
>
> Following is a courtesy copy of the pending claims, showing changes relative to the prior pending version."

The current amendments, provided with this submission, are in accordance with 37 CFR §1.173 (pages 2-3 of this submission); a courtesy copy is also provided with the amendments made in accordance with 37 CFR §1.121 (pages 4-5).

III. Claim Objections

As noted above, claim 4 has been amended to correct a typographical error pointed out by the Examiner.

IV. Rejections under 35 USC §251: Reissue Oath/Declaration

The pending claims were rejected under 35 USC §251 as being based upon a defective reissue declaration. The Examiner contended that the declaration did not specifically state a

correlation between specified claims and the error relied upon to support the reissue application.

Although the applicant believes that a specific error was in fact identified in the Supplemental Declaration filed on October 7, 2004, a further signed Supplemental Reissue Application Declaration, which more clearly identifies the correlation between specified claims and the error, is enclosed.

V. Rejections under 35 U.S.C. §103(a)

Independent claim 5 and dependent claim 6 were again rejected under 35 U.S.C. §103(a) as being unpatentable over Wang *et al.* (EP 0304845) in view of Hornes *et al.* (U.S. Patent No. 5,512,439). The rejections are respectfully traversed in light of the following remarks.

A. The Invention

The applicant's invention, as embodied in independent claim 5, is directed to a composition of matter comprising a plurality of from ten thousand to a hundred thousand different polynucleotides. The composition includes a mixture of microparticles, wherein each microparticle has identical polynucleotides of the plurality attached thereto, and wherein substantially all different polynucleotides in the plurality are attached to different microparticles. In accordance with dependent claim 6, the number of identical polynucleotides attached to each microparticle may be 10^4 - 10^5.

B. Analysis

The rejection is based on the reasoning that the combined teachings of Wang and Holmes could be used "to provide a composition comprising a plurality of polynucleotides, where 10^4 to 10^5 polynucleotides are attached to different microparticles" (page 5 of Office Action). However, the present claims do not recite simply "a plurality of polynucleotides". The claims recite "a plurality *of from ten thousand to a hundred thousand different* polynucleotides." Moreover, the claims do not recite that "10^4 to 10^5 polynucleotides are attached to different microparticles", but rather that each microparticle may contain this number of identical polynucleotides attached.

The Office Action further states (page 4) that "Contrary to Applicants' assertions, Wang

teaches a plurality of probes attached to microparticles, wherein the plurality of probes comprises sequences that differ from each other". It is not clear how this statement is contrary to the applicants' assertions. As argued previously (responses filed December 9, 2001 and October 7, 2004), Wang describes a "plurality" of such probes attached to microparticles, where a plurality is described in the reference as "several", but it by no means teaches, suggests, or indicates how one could prepare "from ten thousand to a hundred thousand different" such probes attached to different microparticles, in accordance with the present claims. The following is a quotation from the response filed December 9, 2001 (emphasis added):

> Wang describes "labelled microbeads to which gene probe molecules are linked", for use in determining the presence and/or quantity of target sequences in mRNA. The disclosure also teaches that **microbeads may be differently labeled with different trace elements** (e.g. Cr, Fe, Zn, and Ba; see page 4, line 52), and that **differently labeled beads may contain different probes**, so that different assays, e.g. for expression of different oncogenes, may be carried out simultaneously. See e.g. page 4, line 53 to page 5, line 5.
>
> **There is no indication in the reference, however, that the number of different polynucleotides used as "gene probes" would number a thousand or more.** In the Example on page 7, which describes simultaneous assay for expression of *ras* and *myc* oncogenes, the *ras* and *myc* probes are formed "through binding of a poly(G)-extended oncogene probe sequence" to a poly(C)-containing microbead. The formation is further described on page 8 as follows: "A poly(dC)-coated microbead reporter labelled with Ti and a poly(G) extended anti-sense probe for *myc* are mixed....Another poly(dC)-coated microbead reporter, labeled with Cr, and a probe for *ras* are prepared in the [same] way." The probes are then contacted with an mRNA sample for the assay.
>
> In this example, **two different polynucleotides** are attached to microbeads. While the reference teaches the use of "**several**" differently labeled microparticles bearing different probes (page 4, lines 47-48) (and one could even conceive that

multiple sequences could be used for probing expression of an oncogene, rather than just one), there is **clearly no disclosure of "a thousand or more" different sequences in a microbead population, where "substantially all different polynucleotides in the plurality are attached to different microparticles."'**

The following is a quotation from the previous response, filed October 7, 2004 (emphasis added):

"...the cited art **does not teach or suggest how one would make or use a composition comprising thousands of different probes, each on a different microparticle.** "In order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method." *Beckmann Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 13 USPQ2d 1301 (Fed. Cir. 1989), quoted in *Motorola, Inc. v. Interdigital Technology Corp.*, 121 F.3d 1461, 43 USPQ2d 1481 (Fed. Cir. 1997) and *Rockwell International Corp. v. United States*, 147 F.3d 1358, 47 USPQ2d 1027 (Fed. Cir. 1998).

Moreover, in Wang's discussion of assays employing different probes, it is necessary that **microparticles having different probes are distinctly labeled (e.g., "several assays can be performed in a single procedure by using several corresponding trace elements";** "the differently labeled microbeads can be separately detected"; page 4, lines 47-56**). There is no teaching of how one would supply thousands of distinct labels to label thousands of different probes.** As described in the passage cited above, the distinct labels in Wang *et al.* are preferably different heavy metal atoms, of which there is a limited supply. Accordingly, one skilled in the art would not envision the use of thousands of different probes from the teachings of Wang *et al.*"

The teaching in Hornes *et al.* that a magnetic particle can carry $10^3 - 10^6$ probe molecules is not relevant to the number of *different polynucleotides* in the claimed

microparticle-supported population, which in accordance with the claims, is "ten thousand to a hundred thousand".

Accordingly, Wang *et al.* and Hornes *et al.* in combination do not suggest the applicant's composition, nor do they suggest how such a composition could be prepared.

In view of the foregoing, the applicant respectfully requests the Examiner to withdraw the rejection under 35 U.S.C. §103(a).

VI. Rejections under 35 USC §251: Recapture

Claim 9 was rejected under 35 USC §251 as directed to an improper recapture of broadened claimed subject matter surrendered in the application for the patent upon which the reissue is based. The Examiner stated that the broadening aspect of these claims was surrendered by the applicant during the prosecution of the '413 patent, in view of the Examiner's description of allowable subject matter in the prosecution of that patent.

In the prosecution of the '413 patent, the Examiner's description of allowable subject matter, in the Office Action dated March 19, 1996, discussed the teachings of two cited references, Chetverin *et al.* and Brenner *et al.* The Examiner in the '413 patent stated that:

> ...The reference [Chetverin *et al.*] does not teach or suggest attaching oligonucleotide tags to the polynucleotides and sorting on the sole basis of the attached "hybridization tag" by hybridization to the tag complement....The reference [Brenner *et al.*, *PNAS* **89**:5381-3, 1992] teaches that to decrease the background of mispairing between a given tag and an imperfect tag complement that the tags should comprise a plurality of subunits of 3-6 nucleotides wherein each subunit of the plurality would have at least one mismatch when paired with the complements of the other subunits of the plurality. The reference does not suggest increasing the minimum number of mismatches...

The applicant made no comment on this statement that is of record in the application.

The undersigned has carefully reviewed the cited Brenner *et al.* reference and has

determined that it does not, in fact, teach that "tags should comprise a plurality of subunits of 3-6 nucleotides wherein each subunit of the plurality would have at least one mismatch when paired with the complements of the other subunits of the plurality". However, while this fact may be pertinent to the patentability of the claims, it is not directly relevant to the issue of recapture.

The following is an excerpt from MPEP §1412.02, "Recapture of Canceled Subject Matter", page 1400-17 (May 2004 Revision; emphasis in original):

> Who can make the surrendering argument?
>
> Assume that the limitation A omitted in the reissue claims was present in the claims of the original application. The examiner's reasons for allowance in the original application stated that it was that limitation A which distinguished over a potential combination of references X and Y. Applicant did not present on the record a counter statement or comment as to the examiner's reasons for allowance, and permitted the claims to issue.
>
> *Ex parte Yamaguchi*, supra, held that a surrender of claimed subject matter cannot be based solely upon an applicant's failure to respond to, or failure to challenge, an examiner's statement made during the prosecution of an application. Applicant is bound only by applicant's revision of the application claims or a positive argument/statement by *applicant*. An applicant's failure to present on the record a counter statement or comment as to an examiner's reasons for allowance does not give rise to any implication that applicant agreed with or acquiesced in the examiner's reasoning for allowance. Thus, the failure to present a counter statement or comment as to the examiner's statement of reasons for allowance does not give rise to any finding of surrender. **The examiner's statement of reasons for allowance in the original application cannot, *by itself*, provide the basis for establishing surrender and recapture.**
>
> It is only in the situation where applicant does file comments on the statement of reasons for allowance, that surrender may have occurred.

In the prosecution of the original application, applicant did not submit comments on the Examiner's statement of reasons for allowance. Accordingly, surrender by applicant did not occur.

The foregoing is further supported by the flow chart on page 1400-22 of the MPEP,

where one of two conditions must be met to support the presence of recapture: either "an amendment was made to narrow the claims, to overcome an art rejection of record", or "an argument or a statement was made *by applicant* that a specific claim limitation defined over the art of record" (emphasis added). Neither of these conditions are met in the present case.

Accordingly, no basis to support an improper recapture of broadened claimed subject matter has been presented.

VII. Rejections under 35 USC §112, second paragraph

The pending claims were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In one particular, the Examiner objected to the term "spacially discrete regions".

Applicants submit that one skilled in the art would understand the conventional meaning of the term "discrete", e.g. "consisting of unconnected distinct parts" (American Heritage® Dictionary of the English Language, Fourth Edition). The concept of "spacially discrete regions", with respect to solid supports for polynucleotides, is further described in the specification, at, for example, column 3, lines 35-44 of the '413 patent:

> In this embodiment, complements of the oligonucleotide tags are synthesized on the surface of a solid phase support, such as a microscopic bead or a specific location on an array of synthesis locations on a single support, such that populations of identical sequences are produced in specific regions. That is, the surface of each support, in the case of a bead, or of each region, in the case of an array, is derivatized by only one type of complement which has a particular sequence.

The Examiner also objected to the phrase "a uniform population of substantially identical oligonucleotide tag complements" in claim 1. As noted above, this phrase has been amended for clarity to "a population of identical oligonucleotide tag complements". Oligonucleotide tags and tag complements are discussed in the specification at length, e.g. at

columns 5-9 of the '413 patent.

The claim term "fragments of a target polynucleotide" in claim 5 has been amended to "fragments of a target polynucleotide to be analyzed or sequenced", per the patent specification at, for example, column 3, lines 5-7, to more clearly define what is intended by the term "target". The other terms in this phrase appear to be unambiguous. One skilled in the art would understand what constitutes a fragment of a polynucleotide and how such fragments can be produced; e.g. via restriction enzymes. Conventional methods of fragmenting a polynucleotide for analysis are also described at column 22 of the '413 patent, and example 2 notes that fragmenting can be done by sonication (column 25, line 45).

Claim 5 is further amended to state that "each microparticle has identical polynucleotides of the plurality attached thereto". This condition is not inconsistent with the condition that "substantially all different polynucleotides in the plurality are attached to different microparticles."

As noted above, the language of dependent claim 6 has been amended to comport more closely with that of parent claim 5. Therefore, the usages of the terms "microparticle" and "polynucleotides", as they relate to the parent claim, should be clear.

Claim 9 has been amended to address the issues of clarity and antecedent basis raised on page 8 of the Office Action.

In view of the foregoing, the applicants submit that the pending claims comply with the requirements of 35 U.S.C. §112, second paragraph.

VIII. Rejections under 35 U.S.C. §112, First Paragraph

The pending claims were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claim terms specifically noted were "a population of identical oligonucleotide tag complements" (as amended), "fragments of a target polynucleotide" and "one or more spatially discrete regions". The rejections are traversed for the following reasons.

As noted above, the concept of "spacially discrete regions" is discussed in the

specification at, for example, column 3, lines 35-44 of the '413 patent. Such a region can be "a microscopic bead" or "a specific location on an array of synthesis locations on a single support". Such supports, and preparation of tags or tag complements on such supports, are also discussed in detail at columns 8 and 12-14 of the '413 patent.

Oligonucleotide tags and tag complements are themselves described in detail at columns 6-9 of the '413 patent; methods of attaching tags to polynucleotides to be sorted, and subsequent sorting onto supports, are described at columns 14-16. Working examples of such processes are provided at columns 23-25.

With respect to the "size and structure" of the "fragments of a target polynucleotide", conventional methods of fragmenting a polynucleotide for analysis are described at column 22 of the '413 patent. Example 2 notes that fragmenting can be done by sonication (column 25, line 45), and that in this case fragments of 300-500 basepairs were produced. In general, one skilled in the art would know how to prepare a cDNA library or how to prepare fragments of a polynucleotide. (Information which is well known in the art need not be described in detail in the specification. See, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986); MPEP §2163(II)(A)(2)). The "structure" of the fragments, e.g. the base sequence, would clearly depend on the polynucleotide being analyzed and is not critical to the claimed composition.

Further support for applicants' possession of the claimed invention is provided by working Example 2, at column 24, line 65 to column 25, about line 60, which describes the preparation of a microparticle-supported polynucleotide composition, in accordance with the claims. Specifically, the Example describes the preparation of a repertoire of oligonucleotide tags, ligation of the tags into a vector (col 25, lines 29-30), preparation of a repertoire of tag complements on microparticles (col 25, lines 31-32), preparation of tagged polynucleotide fragments (by fragmenting followed by ligation into the tag-containing vectors), and hybridization of the tagged fragments onto the tag complements on the microparticles (col 25, lines 58-62), thereby producing a population of identical polynucleotide fragments on each microparticle.

In view of the foregoing, the applicants submit that the pending claims comply with the requirements of 35 U.S.C. §112, first paragraph.

IX. Conclusion

In view of the foregoing, the applicant submits that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

Respectfully submitted,

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